UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/545,199	04/06/2000	David E. Lowery	28341/6227.1NCP	9014

7590 09/23/2002

Joseph A Williams Jr
Marshall O'Toole Gerstein Murray and Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, IL 60606-6402

EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	19

DATE MAILED: 09/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/545,199	Applicant(s) Lowery et al
	Examiner P rtner	Art Unit 1645

-- The MAILING DATE of this communicati n appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 1, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-24, and 31-33* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-24, and 31-33* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1,7 and 31 have been amended.

Claims 2, 25-30 and 34-51 have been canceled.

Claims 1, 3-24 and 31-33 are under consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections Withdrawn

2. In light of the amendment of page 19, lines 25-32 and page 21, Table B, lines 7-17 and 19, through the insertion of commas to indicate that are separate entities, the objection is herein withdrawn.
3. In light of the amendment of pages 37-38, under the column labeled "LD 50", the numbers 104, 105 and 106 have been so amended to obviate the objection through the recitation of consistent disclosure.
4. Claims 7-24 and 31-33 rejected under 35 U.S.C. 112, first paragraph (scope), because the specification, while being enabling for the introduction of mutations into specific open reading frames, specifically the elected SEQ ID NO 3, for the production of an immunogenic recombinant bacteria, does not reasonably provide enablement for formulation of vaccines for any gram negative bacteria, with any mutation in SEQ ID NO 3 or a species homolog of SEQ ID No 3 for the induction of a protective immune response, in light of the amendment of the claims to recite an attenuated Pasteurellaceae bacteria with a mutation in the atpG coding sequence.
5. Claims 1, 3-24, 31-33 rejected under 35 U.S.C. 112, second paragraph recite non-elected inventions and therefore do not distinctly claim Applicant's invention, in light of the amendment of claim 1 and 7 to define the mutation to be in the atpG coding region.

6. Claims 3, 9,15, 21 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "an inactive gene product" in light of the amendment of claim 1 to define the mutation to be in the atpG coding sequence.
7. Claims 4 rejected under 35 U.S.C. 112, second paragraph are dependent claims that recites the phrase "deletion of all or part of said gene" , in light of the amendment of claim 1, to recite the phrase "decreased expression".
8. Claims 6, 12, 18, and 24 rejected under 35 U.S.C. 112, second paragraph are dependent claims and define the mutation to be "an insertion in the gene", in light of the amendment of claim 1 to define the mutation to be in the atpG coding sequence.
9. Claims 8, 14, 20 rejected under 35 U.S.C. 112, second paragraph recite the phrase "decreased expression of a gene product", in light of claim 7 having been amended to no longer recite this phrase, but has been amended to recite "decreased activity".
10. Claims 10, 16, 22 rejected under 35 U.S.C. 112, second paragraph are dependent claims that recites the phrase "deletion of all or part of said gene" while the independent claims require the expression of the gene product with activity (claims 10, 16 and 22), in light of the amendment of claim 7 to recite the phrase "decreased activity".
11. Claims 5, 11, 17, 23 rejected under 35 U.S.C. 112, second paragraph are dependent claims and define the mutation to be a deletion of a gene, in light of the amendment of both claims 1 and 7 to recite differing types of mutations effecting expression and activity, respectively.
12. Claims 31-33 rejected under 35 U.S.C. 112, second paragraph for depending from claims non-elected and withdrawn from consideration, in light of the cancellation of the non-elected and withdrawn claims by amendment herein.
13. Claim 13 rejected under 35 U.S.C. 112, second paragraph for reciting non-elected species, in light of Applicant's arguments.
14. Claims 1-2, 6, 7-8, 12, 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Gwinn et al (Dec. 1997), in light of the amendment of the claims to recite a specific mutation in atpG coding sequence.

Rejections Maintained

15. Claims 1,3-6 and 31-33 rejected under 35 U.S.C. 112, first paragraph (scope, vaccine), because the specification, while being enabling for the introduction of mutations into specific open reading frames, specifically the elected SEQ ID NO3, for the production of an immunogenic recombinant bacteria, does not reasonably provide enablement for formulation of vaccines for any gram negative bacteria, with any mutation in SEQ ID NO 3 or a species homolog of SEQ ID No 3 for the induction of a protective immune response, the full genus of which has not been enabled as vaccine compositions, for reasons of record in paper number 15, paragraph 8.

16. Claims 1, 3-33 rejected under 35 U.S.C. 112, first paragraph (written description, scope), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record in paper number 15, paragraph 9.

17. Claims 1, 3-24, 31-33 rejected under 35 U.S.C. 112, second paragraph reciting the phrase "a gene", that evidences decreased expression, in light of the claims still reciting the term homolog and expression of the homolog gene product which has not been defined; for reasons of record in paper number 15, paragraph 10, page 11, second paragraph.

18. Claims 1, 3-24, 31-33 rejected under 35 U.S.C. 112, second paragraph in light of the mutation in the homolog gene.and gene product, which results in decreased expression, are not clearly set forth in the claims, for reasons of record in paper number 15, paragraph 10.

19. Claims 8, 14, 20 rejected under 35 U.S.C. 112, second paragraph depend from claim 7, and define the mutation to result in "decreased activity of the gene product". A mutation that results in "decreased expression of a gene" would not necessarily result in reduced activity of the gene product, but could result in a gene product that is fully active, but just produced at a lower level. The rejection is maintained for reasons of record in paper number 15, paragraph 10.

20. Claims 1, 3-5, 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamoto et al (1993) for reasons of record in paper number 15, paragraph 12.

Response to Arguments

21. Applicant's arguments filed June 27, 2002 have been fully considered but they are not persuasive.

22. The rejection of claims 1,3-6 and 31-33 under 35 U.S.C. 112, first paragraph (scope, vaccine directed to homolog mutations, any gram negative bacterium with a atpG mutation, or homolog mutation), because the specification, while being enabling for the introduction of mutations into specific open reading frames, specifically the elected SEQ ID NO3, for the production of an immunogenic recombinant bacteria, does not reasonably provide enablement for formulation of vaccines for any gram negative bacteria, with any mutation in SEQ ID NO 3 or a species homolog of SEQ ID No 3 for the induction of a protective immune response, the full genus of which has not been enabled as vaccine compositions, is traversed on the grounds "The disclosure in the specification in combination with what was known in the art as of the priority date clearly provides more than sufficient guidance for the production of vaccine compositions derived from bacteria with mutation in the atpG gene".

23. It is the position of the examiner that scope of enablement rejection was directed to the fact that evidence was made of record showing that NOT all compositions of attenuated

bacteria induce a protective immune response. Attenuated strains of bacteria are not always safe and have been found to induce systemic disease. In addition to the unpredictability of vaccines discussed in the first Office action, the examiner made of record a published reference to Humbert et al that teaches through a defective gamma subunit in the ATP synthase of a gram negative bacteria (E.coli) actually developed antibiotic resistance, a characteristic that would help the bacteria to avoid treatment and eradication of infection using traditional means. Humbert et al provide evidence that a mutation in the atgG coding sequence would not always result in a composition of bacteria that would have characteristics of a vaccine strain of bacteria.

The scope of enablement rejection over claims directed to vaccines is maintained for reasons of record. Amendment of the claims to be directed to the scope of the invention enabled by the instant specification could obviate this rejection.

24. The rejection of claims 1, 3-33 under 35 U.S.C. 112, first paragraph (written description, scope), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is traversed on the grounds that "the written description analysis that is specifically applicable for nucleic acids and that this analysis is not appropriate for all "genus" subject matter. The claimed invention relates to attenuated gram negative bacteria and vaccine compositions

comprising the bacteria and not t polynucleotides per se." and concludes that "There is not need to precisely define the chemical structure of every atpG gene in every bacteria or vaccine".

25. It is the position of the examiner that the patentable novelty of the instant Application is directed to mutations in a polynucleotide sequence that encodes for the gamma subunit of ATPase of Pasteurella moltocida, that is taught to have a possible, potential, gene function of atpG (see Table 1, page 37, instant specification, bottom of page) and SEQ ID No 132, obtained from Actinobacillus pleuropneumoniae. The claimed invention is directed mutations that effect gene products. Clearly the instantly claimed invention is directed to subject matter that is specifically applicable for nucleic acids. The written description analysis set forth in the First Office action is clearly applicable to the claimed invention that is directed to atpG genes in gram negative bacteria not described or known in the art, as well as homolog gene coding sequences not described, the gene products not defined to have any specific homologous function.

With respect to defining a representative number of species to describe the now claimed genus of mutated gram negative bacteria, it is the position of the examiner that no specific genes (open reading frames) that encode species homologs of the identified nucleic acid sequences meet the written description requirement by providing a representative number of species of the claimed genus recombinant bacteria with mutations in species homologs of nucleic acid sequences of SEQ Id No 3 and are mutated to evidence reduced gene product activity,

and/or reduced expression of the encoded gene product. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating the nucleic acid molecule. The nucleic acid that encodes the gene product itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. The rejection is maintained for reasons of record. Amendment of the claims directed to material that has been described in the instant specification could obviate this rejection.

26. The rejection of claims 1, 3-24, 31-33 under 35 U.S.C. 112, second paragraph for reciting the phrase "a gene", is asserted to have been obviated through amendment of the claims to recite "a mutation in the atpG protein coding region of SEQ ID No 3".

27. It is the position of the examiner that this rejection was partially obviated through amendment of the claims to recite the phrase "a mutation in the atpG protein coding region of SEQ ID No 3", but the claims still recite the phrase "or species homologs thereof" and the phrase "a gene product encoded by the mutated gene". While it is clear that within the scope of the claims there is now a defined gene product of atpG, what the "species homolog" is and what the species homolog "gene product" is, is still unclear. Why doesn't the claim define the gene product to be an atpG gene product? What other homolog gene products are intended by the claim? Are other coding sequences of the ATP operon intended to be atpG homologs? The claimed invention is still unclear,

though the amendment partially obviated the rejection, that portion of the rejection that has not been obviated is maintained for reasons of record.

28. The rejection of claims 1, 3-24, 31-33 rejected under 35 U.S.C. 112, second paragraph, for the recitation of the phrase "decreased activity of a gene product"(claims 7-24 and 31-33, and questioned with respect to what gene product must be expressed (claims 1, 3-6 and 31-33 have been amended to recite "decreased expression) is traversed on the grounds that the claims have been amended to recite that the mutation is in the atpG coding sequence which clarifies what the gene product and what must be expressed.

29. It is the position of the examiner that through amendment of the claims to recite the phrase "a mutation in the atpG protein coding region", the rejection under 112, second paragraph was partially obviated, but what gene and what gene product must evidence decreased activity or decreased expression is not distinctly claimed, because what the genes are that are the intended homologs is not clearly set forth in the claims.

30. The rejection of claims 8, 14, 20 under 35 U.S.C. 112, second paragraph, for reciting that a single mutation would result in "decreased activity of the gene product" and result in "decreased expression of a gene" is traversed on the grounds that "the dependent claims are further limitations of the decrease in activity, not additional mutations", that "a decrease in expression of a gene product does reduce the overall activity of the gene

product in some manner, be it inherent enzymatic activity or subsequent downstream activity" and "a decrease in gene expression could result from a mutation which almost completely abolishes gene expression, thereby resulting in no gene product being produced and thus no activity".

31. It is the position of the examiner that through the recitation of "decreased activity (claim 7)" the claims include within the scope, gene expression of a product with activity and gene expression product without activity. The dependent claims which recite that the mutation effects expression of the gene product, resulting in decreased expression, need not be limited to decreased expression equals decreased activity, but includes within the scope an additional mutation of the promoter so that the amount of expressed product is reduced. While Applicant's arguments are clear, the claimed invention is not. An amendment of the claim to recite a phrase that sets forth the concept

--wherein the activity is decreased due to decreased gene expression-- rather than setting forth claim limitations that redefine the mutation to be one that effects expression rather than activity could obviate this rejection. A bacterium with a plurality of mutations, clearly supported by the specification could be claimed as having more than one mutation. While expression can influence product activity, the claim language recited does not show a clear delineation as to what type of mutation is being introduced into the claimed bacterium.

32. The rejection of claims 1,3-5, 31-32 under 35 U.S.C. 102(b) as being anticipated by Nakamoto et al (1993) is respectively traversed on the grounds that "Nakamoto describes a mutated E.coli atpG gene which results in a decrease in ATPase activity, but does not address the protein expression levels resulting from the outlined mutation".

33. It is the position of the examiner that Nakamoto et al does disclose a gamma subunit deficient strain of E.coli, a gram negative bacteria (see page 868, col. 1, Bacterial strain and Growth conditions section), when the strain is deficient in the gamma subunit, no gamma subunit would be expressed, thus there would be decreased expression of the encoded ATP gamma subunit, because not coding sequence is present in this strain of E.coli.

It is also the position of the examiner that Nakamoto et al disclose mutant strains of gram negative bacteria that evidence mutations that prevent the assembly of mature ATP synthase, thus preventing expression of the gene product, the product being an active ATP synthase. The encoded gene product without assembly into ATP-synthase would be inactive gene product, thus defining decreased expression of the gene product that is active (see page 867, col. 2, paragraph 2). In addition to the gamma subunit deficient strain of E.coli, the reference also discloses a E.coli, strains with site-directed mutations at the carboxyl-terminal of the gamma subunit, in the conserved amino acids, which resulted in an ATPase with lower activity (see page 867, col. 2, paragraph 2, last two sentences). The rejection is maintained for reasons of record.

New Claim Limitations/New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 112

34. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35. Claims 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31-33, specifically claim 31 has been amended to depend from any one of claims 1-24, and claims 32-33 depend from claim 31. Applicant canceled claim 2; claims 31-33 depends from a canceled claim.

Conclusion

36. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

September 20, 2002

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600